AWARD NUMBER: W81XWH-15-1-0675

TITLE: A Randomized, Double-Blind, Placebo-Controlled Crossover Study of the Anti-Inflammatory Compound Anatabine to Treat Pain in GWI Patients**.**

PRINCIPAL INVESTIGATOR: Dr. Fiona Crawford

RECIPIENT: Roskamp Institute
Sarasota, FL 34243

REPORT DATE: December 2018

TYPE OF REPORT: Final

Early Termination

PREPARED FOR: U.S. Army Medical Research and Materiel Command
Fort Detrick, Maryland 21702-5012

DISTRIBUTION STATEMENT: Approved for Public Release; Distribution Unlimited

REPORT DOCUMENTATION PAGE

Form Approved
OMB No. 0704-0188

1. REPORT DATE: ***Dec 2018*** **2. REPORT TYPE: Final**	**3. DATES COVERED:** 30Sep2015-29Sep2018
4. TITLE AND SUBTITLE: A Randomized, Double-Blind, Placebo-Controlled Crossover Study of the Anti-Inflammatory Compound Anatabine to Treat Pain	**5a. CONTRACT NUMBER** **W81XWH-15-1-0675**
	5b. GRANT NUMBER
	5c. PROGRAM ELEMENT NUMBER
6. AUTHOR(S): Fiona Crawford, Ph.D.	**5d. PROJECT NUMBER**
	5e. TASK NUMBER
Email: fcrawford@roskampinstitute.org	**5f. WORK UNIT NUMBER**
7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES) AND ADDRESS(ES) The Roskamp Institute, Inc. 2040 Whitfield Avenue Sarasota, Florida, 34243-3922	**8. PERFORMING ORGANIZATION REPORT**
9. SPONSORING / MONITORING AGENCY NAME(S) AND ADDRESS(ES) U.S. Army Medical Research and Material Command Fort Detrick, Maryland 21702-5012	**10. SPONSOR/MONITOR'S ACRONYM(S)**
	11. SPONSOR/MONITOR'S NUMBER(S)

12. DISTRIBUTION / AVAILABILITY STATEMENT: Approved for Public Release; Distribution Unlimited

13. SUPPLEMENTARY NOTES

14. ABSTRACT: The goal of the proposed clinical trial was to target one of the major complaints from veterans with Gulf War Illness (GWI) - namely chronic pain and inflammation - using a compound with a history of safe use in humans and efficacy in an animal model of GW agent exposure. Musculoskeletal pain and associated inflammation are some of the most debilitating symptoms of GWI, and the national War Related Illness and Injury Study Centers (WRIISC) report pain as the major complaint from GW veterans (90%), exceeding the next most prevalent symptom, fatigue, by three fold. Identifying effective, safe, and tolerable treatments will alleviate major aspects of the currently untreatable multisymptom condition.

Our GWI research program has developed and characterized a mouse model of exposure to the GW agents Pyridostigmine Bromide and Permethrin. Following a 10 day exposure, we investigate chronic changes in behavior, over months and years, in the brain and the blood, to identify cellular mechanisms and functions that have been disrupted as a consequence of the exposures, and which we may target with therapeutic approaches. Our work has demonstrated an evolving and persistent inflammation in these animals, consistent with the reports and complains from GWI patients. We have noted behavioral and cognitive changes in mice following these exposures. Over the last few years we have carried out extensive work on the dietary supplement Anatabine (Rock Creek Pharmaceuticals Inc.(RCP)), which is a naturally occurring compound found in tobacco, tomatoes, eggplant and peppers. Our work has shown that it has strong anti-inflammatory properties. Based on sales, an estimated 300,000-500,000 individuals used these products with positive effects on pain alleviation and only minor adverse effects reported. We have conducted clinical studies of anatabine in healthy human subjects which demonstrated its safety and tolerability. In our GWI mouse model anatabine improved behavioral symptoms and reduced inflammation.

Therefore, we proposed a clinical evaluation of anatabine in a small population of GWI patients, comprising 11 weeks of treatment and 11 weeks of placebo (or vice-versa) and an evaluation of the effects on Pain and other related conditions. This would have been the first time that data from a laboratory model of GWI was partnered with a human study to support a potential GWI treatment, thus providing proof of concept for the GWI preclinical models. If successful then this trial would have led to a larger trial of several hundred GWI patients across multiple sites, which in turn would support an application to the Food and Drug Administration (FDA) for anatabine as a treatment for GWI. Given the extreme prevalence of chronic pain in the GWI patient population we believe that anatabine could benefit most GWI patients, and mitigate the use of other potentially addictive pain relievers. Targeting inflammation may have beneficial effects on many aspects of GWI, and this work could have led to investigation of other anti-inflammatory compounds. Unfortunately, due to an FDA hold and the concomitant delays, we were unable to begin the trial in a timely fashion, and RCP went out of business and are no longer in a position to provide the investigational product and placebo required for this study, even if FDA approval were now granted.

15. SUBJECT TERMS None Listed

16. SECURITY CLASSIFICATION OF:			**17. LIMITATION OF ABSTRACT**	**18.NUMBER OF PAGES**	**19a. NAME OF RESPONSIBLE PERSON:** USAMRMC
a. REPORT U	**b. ABSTRACT** U	**c. THIS PAGE** U	U	14	**19b. TELEPHONE NUMBER** ***(include area code)***

Standard Form 298 (Rev. 8-98)

TABLE OF CONTENTS

1. INTRODUCTION:

Hypothesis: Daily administration of Anatabine, a potent and safe anti-inflammatory compound, will improve symptoms of pain and fatigue in patients with GWI and may also improve cognitive function.

Aim 1: To conduct a double-blind, Placebo-controlled crossover study of the effects of Anatabine in a GWI patient population.
Aim 2: To determine if anatabine treatment mitigates the chronic pain suffered by GWI patients
Aim 3: To determine if anatabine treatment is associated with improvements in mood and/or cognitive function in GWI patients
Aim 4: To collect and analyze blood samples from subjects pre- and post- each phase of treatment to quantify anatabine levels and to evaluate treatment-dependent changes in markers of inflammation.

The most important activity for this project is to obtain approval from the FDA to conduct the proposed trial. As detailed below, we prepared and submitted the IND, and have been placed on clinical hold, awaiting our ability to respond to their enquiries regarding our application.

With regard to the other regulatory actions required to begin this project - namely IRB approval and site approval - we have a draft protocol and consent from for the study, and are planning to schedule a visit from our co-investigator Dr. Krengel, but progress with these actions is pending FDA approval.

Dr. Crawford participated in a GWI symposium at the International Neuropsychological Society meeting in London in July 2016, organized by Dr. Kim Sullivan. Other participants included Drs. Maxine Krengel and Julia Golier. Drs. Krengel, Sullivan and Golier are all involved with the proposed clinical trial, either as co-investigators or consultants, and so this meeting afforded the opportunity for some discussion regarding the response to the FDA and assurance of continued enthusiasm for the project and the trial by all parties concerned.

2. KEYWORDS:

Gulf War Illness; Anatabine; Inflammation; Pain; Fatigue; Cognition

3. ACCOMPLISHMENTS:

The PI is reminded that the recipient organization is required to obtain prior written approval from the awarding agency Grants Officer whenever there are significant changes in the project or its direction.

What were the major goals of the project?
List the major goals of the project as stated in the approved SOW. If the application listed milestones/target dates for important activities or phases of the project, identify these dates and show actual completion dates or the percentage of completion.

1. Submission of Investigator Initiated Investigational New Drug Application to the FDA on December 2nd, 2015.
2. A request for additional information regarding the preclinical data and the proposed study design was received on December 15th, 2015 and our response was submitted on December 17th, 2015.
3. Notification of being placed on "clinical hold" was received, by telephone, on December 30th,
2015.
4. The FDA clinical hold letter was received in January with questions relating to anatabine and to the previous preclinical studies and their relevance/pertinence to the proposed trial. We had extensive discussions with the company Rock Creek Pharmaceuticals (manufacturers of anatabine, and committed providers of product for the trial) to determine how best to address the FDA questions.
5. One of the issues stated in the FDA clinical hold letter was the fact that preclinical studies with the same formulation proposed in our clinical trial had Not been carried out for the duration of study proposed in our clinical trial. Thus the FDA was suggesting that we either present preclinical data supporting our clinical trial design or, potentially, we could have suggested modification to our clinical trial design to fit what had previously been accomplished preclinically.

What was accomplished under these goals?
For this reporting period describe: 1) major activities; 2) specific objectives; 3) significant results or key outcomes, including major findings, developments, or conclusions (both positive and negative); and/or 4) other achievements. Include a discussion of stated goals not met. Description shall include pertinent data and graphs in sufficient detail to explain any significant results achieved. A succinct description of the methodology used shall be provided. As the project progresses to completion, the emphasis in reporting in this section should shift from reporting activities to reporting accomplishments.

As per our Statement of Work –

Specific Aim 1: To conduct a double-blind, placebo controlled crossover study of the effects of Anatabine in a GWI patient population.

Major Task 1: IRB approval (months 1-3)
Preparation of documents is in progress but will not be finalized and submitted to the IRB until FDA approval has been obtained.

Major Task 2: FDA approval (months 1-6)
We prepared a very detailed Investigator Initiated IND, which was submitted on December 2nd, 2015. Prior to submission, Dr. Crawford had several conversations and communications with Dr. Sandy Barnes of the FDA in the Division of Pulmonary, Allergy, and Rheumatology Products, the division to which our II-IND was to be submitted.

The investigational product for our trial is Anatabine, a potent anti-inflammatory compound, which was available from Rock Creek Pharmaceuticals (RCP) for several years (2010-2014) as a dietary supplement. It is no longer being sold as a dietary supplement, as the company was going to pursue an IND with the FDA for its use as a pharmaceutical.

However, the company withdrew its IND application to pursue trials with the product in Europe. Thus, in the US, anatabine is neither a dietary supplement nor a pharmaceutical, and so there was no IND to which we or the FDA could refer in relation to our application.

In discussing this situation with Dr. Barnes she indicated that I should provide as much information as possible, including a detailed CMC section, explaining that the batch of product for the proposed trial would be made in exact accordance with that methodology and those specifications. We had the full support of RCP in our submission of the IND (RCP have agreed to provide us with the product and matched placebo for the study, free of charge) and so we were able to include RCP's most recent Investigator's Brochure (dated November 2014) which contains all of the preclinical and clinical data available at that time, as well as the extensive safety and exposure data from the use of anatabine as a dietary supplement.

Furthermore, RCP provided us with pre-final-report data from its recently conducted trial in the UK to support the safety and tolerability of anatabine at doses above those proposed in our trial.

As previously reported, I believe that our approximately 600 page II-IND submission provided considerably more detail regarding the proposed investigational product than is usual for an II-IND. We received questions by mail, from Dr. LeAnn Brodhead of the same FDA Division, on Tuesday December 15th, 2014, with response required by 17.00 on Thursday December 17th, pertaining to the preclinical studies and our trial design. We responded in detail in the timeframe required, and as the questions made reference to the FDA Guidance for Industry I did also take the opportunity to remind the FDA that ours was an Investigator Initiated IND from a not-for-profit research institute, not a commercial IND. I also reminded them of the devastating impact of GWI to our veterans and the fact that it is considered a debilitating disorder.

On December 30th, 2014, I received a phonecall from Dr. Brodhead informing me that the IND was being placed on clinical hold and that I would receive a letter with detailed information regarding this and how to respond. Having received this letter in January, and given that it suggests requirement for GMP experiments which are beyond the scope of our Institute, we are in discussions with RCP regarding their interest and ability to support provision of such data to the FDA to support our application.

Rock Creek Pharmaceuticals (RCP) went through some management changes in 2013/2014 in the aftermath of some public revelations regarding the inappropriate activities of the former CEO. Despite the best efforts of the new CEO, the financial burden of the ongoing lawsuits ultimately resulted in the bankruptcy of the company. Prior to this RCP had committed to providing the investigational product and placebo required for the proposed trial.

The Roskamp Institute does not have the funds to conduct the required preclinical studies to address the FDA concerns, nor to now shoulder the expenses of GMP manufacture of anatabine product and placebo for the proposed trial.

Major Task 3: Site Preparation (months 1-6)
Our clinic staff are familiar with the protocol, having worked with me on the original submission to the DoD, and since notification of award they have been gaining further knowledge about Gulf War Illness from Institute researchers and from patients to our clinic.

Describe opportunities for training and professional development provided to anyone who worked on the project or anyone who was involved in the activities supported by the project. "Training" activities are those in which individuals with advanced professional skills and experience assist others in attaining greater proficiency. Training activities may include, for example, courses or one-on-one work with a mentor. "Professional development" activities result in increased knowledge or skill in one's area of expertise and may include workshops, conferences, seminars, study groups, and individual study. Include participation in conferences, workshops, and seminars not listed under major activities.

Nothing to Report.

How were the results disseminated to communities of interest?
If there is nothing significant to report during this reporting period, state "Nothing to Report."

Describe how the results were disseminated to communities of interest. Include any outreach activities that were undertaken to reach members of communities who are not usually aware of these project activities, for the purpose of enhancing public understanding and increasing interest in learning and careers in science, technology, and the humanities.

Nothing to Report.

What do you plan to do during the next reporting period to accomplish the goals?
If this is the final report, state "Nothing to Report."

Describe briefly what you plan to do during the next reporting period to accomplish the goals and objectives.

We are unable to move forward with this program, owing to the costs associated with manufacture of Anatabine product and matching placebo, and the preclinical studies required by the FDA. Therefore, despite our ongoing enthusiasm for anatabine as an extremely potent anti-inflammatory which could potentially be of great value to GWI patients, we regretfully close this program as the FDA will not allow us to progress at this time.

4. IMPACT:

What was the impact on the development of the principal discipline(s) of the project?
If there is nothing significant to report during this reporting period, state "Nothing to Report."

Describe how findings, results, techniques that were developed or extended, or other products from the project made an impact or are likely to make an impact on the base of knowledge, theory, and research in the principal disciplinary field(s) of the project. Summarize using language that an intelligent lay audience can understand (Scientific American style).

Nothing to Report.

What was the impact on other disciplines?
If there is nothing significant to report during this reporting period, state "Nothing to Report."

Describe how the findings, results, or techniques that were developed or improved, or other products from the project made an impact or are likely to make an impact on other disciplines.

Nothing to Report.

If there is nothing significant to report during this reporting period, state "Nothing to Report."

Describe ways in which the project made an impact, or is likely to make an impact, on commercial technology or public use, including:

- *transfer of results to entities in government or industry;*
- *instances where the research has led to the initiation of a start-up company; or*
- *adoption of new practices.*

Nothing to Report.

What was the impact on society beyond science and technology?
If there is nothing significant to report during this reporting period, state "Nothing to Report."

Describe how results from the project made an impact, or are likely to make an impact, beyond the bounds of science, engineering, and the academic world on areas such as:

- *improving public knowledge, attitudes, skills, and abilities;*
- *changing behavior, practices, decision making, policies (including regulatory policies), or social actions; or*
- *improving social, economic, civic, or environmental conditions.*

Nothing to Report.

5. **CHANGES/PROBLEMS:** The Project Director/Principal Investigator (PD/PI) is reminded that the recipient organization is required to obtain prior written approval from the awarding agency Grants Officer whenever there are significant changes in the project or its direction. If not previously reported in writing, provide the following additional information or state, "Nothing to Report," if applicable:

Changes in approach and reasons for change
Describe any changes in approach during the reporting period and reasons for these changes. Remember that significant changes in objectives and scope require prior approval of the agency.

As detailed in 1c above, we are currently on clinical hold from the FDA and thus cannot proceed as we do not have the resources to address their concerns or questions.

Actual or anticipated problems or delays and actions or plans to resolve them
Describe problems or delays encountered during the reporting period and actions or plans to resolve them.

Aside from the FDA clinical hold there were no problems that would have impeded the proposed trial; our team was ready and able to conduct the study, and we anticipated good recruitment to the study through our local networks. The doses proposed in our study were below those which have been shown to be safe and well tolerated in previous human studies. At the time of submission we had the support of the company (RCP) which would have manufactured the product and matched placebo to FDA GMP standards, and had we been able to move forward in a timely fashion (i.e. if the FDA had not put us on clinical hold) then we should have been able to have obtained the required product and placebo from RCP and begun our study prior to RCP running into the difficulties which precluded their ongoing participation in this program.

Although the costs associated with conducting this proposed trial were minimal, and supported by The Roskamp Institute, without the support of the pharmaceutics company RCP (Rock Creek Phar

Although the costs associated with conducting this proposed trial were minimal, and supported by the Roskamp Institute, without the support of the pharmaceutical company RCP (Rock Creek

Changes that had a significant impact on expenditures
Describe changes during the reporting period that may have had a significant impact on expenditures, for example, delays in hiring staff or favorable developments that enable meeting objectives at less cost than anticipated.

The majority of effort to date was from Dr. Crawford and her administrative support, in putting together the IND for submission to the FDA, and in negotiations with RCP.

Significant changes in use or care of human subjects, vertebrate animals, biohazards, and/or select agents
Describe significant deviations, unexpected outcomes, or changes in approved protocols for the use or care of human subjects, vertebrate animals, biohazards, and/or select agents during the reporting period. If required, were these changes approved by the applicable institution committee (or equivalent) and reported to the agency? Also specify the applicable Institutional Review Board/Institutional Animal Care and Use Committee approval dates.

Significant changes in use or care of human subjects

Nothing to Report.

Significant changes in use or care of vertebrate animals.

Nothing to Report.

Significant changes in use of biohazards and/or select agents

Nothing to Report.

6. PRODUCTS: List any products resulting from the project during the reporting period. If there is nothing to report under a particular item, state "Nothing to Report."

- **Publications, conference papers, and presentations**
  Report only the major publication(s) resulting from the work under this award.

  Journal publications. *List peer-reviewed articles or papers appearing in scientific, technical, or professional journals. Identify for each publication: Author(s); title; journal; volume: year; page numbers; status of publication (published; accepted, awaiting publication; submitted, under review; other); acknowledgement of federal support (yes/no).*

Nothing to Report.

Books or other non-periodical, one-time publications. *Report any book, monograph, dissertation, abstract, or the like published as or in a separate publication, rather than a periodical or series. Include any significant publication in the proceedings of a one-time conference or in the report of a one-time study, commission, or the like. Identify for each one-time publication: Author(s); title; editor; title of collection, if applicable; bibliographic information; year; type of publication (e.g., book, thesis or dissertation); status of publication (published; accepted, awaiting publication; submitted, under review; other); acknowledgement of federal support (yes/no).*

Nothing to Report.

Other publications, conference papers, and presentations. *Identify any other publications, conference papers and/or presentations not reported above. Specify the status of the publication as noted above. List presentations made during the last year (international, national, local societies, military meetings, etc.). Use an asterisk (*) if presentation produced a manuscript.*

Nothing to Report.

- **Website(s) or other Internet site(s)**
  List the URL for any Internet site(s) that disseminates the results of the research activities. A short description of each site should be provided. It is not necessary to include the publications already specified above in this section.

Nothing to Report.

- **Technologies or techniques**
  Identify technologies or techniques that resulted from the research activities. In addition to a description of the technologies or techniques, describe how they will be shared.

Nothing to Report.

- **Inventions, patent applications, and/or licenses**
  Identify inventions, patent applications with date, and/or licenses that have resulted from the research. State whether an application is provisional or non-provisional and indicate the application number. Submission of this information as part of an interim research performance progress report is not a substitute for any other invention reporting required under the terms and conditions of an award.

Nothing to Report.

- **Other Products**
  Identify any other reportable outcomes that were developed under this project. Reportable outcomes are defined as a research result that is or relates to a product, scientific advance, or research tool that makes a meaningful contribution toward the understanding, prevention, diagnosis, prognosis, treatment, and/or rehabilitation of a disease, injury or condition, or to improve the quality of life. Examples include:
  - *data or databases;*
  - *biospecimen collections;*
  - *audio or video products;*
  - *software;*
  - *models;*
  - *educational aids or curricula;*
  - *instruments or equipment;*
  - *research material (e.g., Germplasm; cell lines, DNA probes, animal models);*
  - *clinical interventions;*
  - *new business creation; and*
  - *other.*

Nothing to Report.

7. PARTICIPANTS & OTHER COLLABORATING ORGANIZATIONS

What individuals have worked on the project?
Provide the following information for: (1) PDs/PIs; and (2) each person who has worked at least one person month per year on the project during the reporting period, regardless of the source of compensation (a person month equals approximately 160 hours of effort). If information is unchanged from a previous submission, provide the name only and indicate "no change."

Example:

Name: *Mary Smith*
Project Role: *Graduate Student*
Researcher Identifier (e.g. ORCID ID): *1234567*
Nearest person month worked: *5*

Contribution to Project: *Ms. Smith has performed work in the area of combined error-control and constrained coding.*
Funding Support: *The Ford Foundation (Complete only if the funding support is provided from other than this award).*

Name: *Fiona Crawford, Ph.D.*
Project Role: *Principal Investigator*
Researcher Identifier (e.g. ORCID ID):
Nearest person month worked: *1.2*
Contribution to Project:
Funding Support:

Has there been a change in the active other support of the PD/PI(s) or senior/key personnel since the last reporting period?
If there is nothing significant to report during this reporting period, state "Nothing to Report."

If the active support has changed for the PD/PI(s) or senior/key personnel, then describe what the change has been. Changes may occur, for example, if a previously active grant has closed and/or if a previously pending grant is now active. Annotate this information so it is clear what has changed from the previous submission. Submission of other support information is not necessary for pending changes or for changes in the level of effort for active support reported previously. The awarding agency may require prior written approval if a change in active other support significantly impacts the effort on the project that is the subject of the project report.

Nothing to Report.

Describe partner organizations – academic institutions, other nonprofits, industrial or commercial firms, state or local governments, schools or school systems, or other organizations (foreign or domestic) – that were involved with the project. Partner organizations may have provided financial or in-kind support, supplied facilities or equipment, collaborated in the research, exchanged personnel, or otherwise contributed.

Provide the following information for each partnership:
Organization Name:
Location of Organization: (if foreign location list country)
Partner's contribution to the project (identify one or more)

- *Financial support;*
- *In-kind support (e.g., partner makes software, computers, equipment, etc., available to project staff);*
- *Facilities (e.g., project staff use the partner's facilities for project activities);*
- *Collaboration (e.g., partner's staff work with project staff on the project);*
- *Personnel exchanges (e.g., project staff and/or partner's staff use each other's facilities, work at each other's site); and*
- *Other.*

Nothing to Report.

8. SPECIAL REPORTING REQUIREMENTS

COLLABORATIVE AWARDS: N/A

QUAD CHARTS: N/A

9. APPENDICES: N/A